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Our current knowledge of the pathophysiology of chronic hibernating myocardium is mainly based on results from clinical studies, because of the absence of appropriate and validated animal models. These clinical observations have given rise to two major controversies: the role of reduced blood flow and that of histological changes in the hibernating segments. In this review, these two subjects will be briefly discussed, and put into the perspective of findings emerging from recently developed animal models. *Coron Artery Dis* 12:381–385 © 2001 Lippincott Williams & Wilkins

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Introduction

In patients with coronary artery disease, chronic reversible left ventricular contractile dysfunction, often referred to as 'chronic hibernating myocardium', is a frequently encountered clinical entity. The reduced left ventricular function in this setting is thought to be an adaptive response to inadequate myocardial perfusion. In this way the myocardium adjusts its metabolic demand to meet the decreased supply, and thus preserves its viability and prevents irreversible injury [1]. Although the concept of hibernating myocardium has an important clinical impact, its underlying pathophysiological mechanisms are largely unknown. Because of the absence of appropriate animal models, current knowledge of chronic hibernating myocardium in man is mainly based on the results of clinical studies, and has led to two major controversies. The first controversy relates to whether the functional abnormalities are a result of chronically reduced myocardial perfusion, on the one hand, or of repetitive episodes of acute ischemia despite normal resting perfusion on the other, that is, whether or not chronic hibernation actually represents chronic repetitive stunning. The second controversy results from the finding of complex structural changes, both cellular and extracellular, in the human hibernating myocardium. Given the severity of these structural changes, it is likely that they affect contractile function. It is, however, not clear whether or not these structural changes are adaptive (and thus reversible). Some observations suggest that they represent the first stage of a degenerative pathway, leading to irreversible damage [2]. In this review, the most important recent findings regarding these two controversies will be briefly focused on.

Histopathology of chronic hibernating myocardium

Several structural abnormalities can be found in transmural needle biopsies from chronic hibernating myocardium, taken during coronary bypass surgery. Concerning cellular changes, perinuclear sarcomere depletion is found in a substantial number of cardiomyocytes, which however do not become atrophic, but instead increase their volume by accumulating glycogen in the sarcomere-depleted perinuclear areas. These cells also display numerous small and abnormally shaped mitochondria, have nuclei with homogeneously dispersed heterochromatin, and lose their well-organized sarcoplasmic reticular system [3]. These changes mean that such cardiomyocytes adopt features that resemble

the fetal phenotype, and suggest that cellular dedifferentiation has taken place. This has been confirmed by the finding of an embryonic/fetal expression pattern of several proteins, such as titin, desmin, cardiotin, and the re-expression of α-smooth muscle actin in these cardiomyocytes [4]. It has been suggested that this process of dedifferentiation represents a kind of programmed cell survival: the cells are transformed from an energy-consuming active contractile phenotype to an energy-saving acontractile phenotype [5]. Indeed, an increased tolerance of dedifferentiated cells to acute ischemia with preservation of mitochondrial oxidative phosphorylation has been shown [6]. Moreover, the role of glycogen storage could have a similar role as in cardiomyocytes during cardiac development, where it has been suggested that glycogen storage plays a crucial role in maintaining a certain degree of turgor, necessary for cell survival [7].

It is likely, although not proven, that these structural changes are reversible. This is suggested by the reversible nature of contractile dysfunction. Because the structural changes are unlikely to be immediately reversible, it is hypothesized that the delay in recovery of function is at least partly attributable to these structural abnormalities [8,9]. However, it must be stressed that both the contribution of the structural changes to the functional abnormalities, and the contribution of the hypothesized reversibility of these changes to the recovery of function, remain to be established. Although it is possible that the functional abnormalities are independent from the structural changes, the recent finding that the rate of functional recovery correlates with the percentage of structurally altered cardiomyocytes, strongly favors such a relationship [9].

The trigger for cardiomyocyte dedifferentiation is unknown. Although dedifferentiated cardiomyocytes are consistently found in biopsies from patients with chronic reversible left ventricular dysfunction, it is not a unique feature of chronic hibernating myocardium. Indeed, the same cellular changes are found in several other cardiomyopathies, such as volume and pressure overload [10], chronic atrial fibrillation in humans [11] and goats [12], in infarct border zones [13], and in explanted failing hearts [14]. A common factor in both chronic hibernation and several of these other cardiomyopathies in which cardiomyocyte dedifferentiation is found, is an increased dilatation of the left ventricular or atrial wall. It is therefore suggested that (moderate) cellular stretch might be involved in triggering cardiomyocyte dedifferentiation. Hibernation-like dedifferentiation characteristics are found in cultured adult rabbit cardiomyocytes undergoing transient and repetitive stretch [15]. These findings suggest at least that a decreased oxygen availability is not *per se* necessary for triggering dedifferentiation. That increased preload-induced stretch may play a role in the induction of the histopathological changes is also suggested in a pig model of chronic hibernating myocardium, in which cardiomyocyte dedifferentiation was not only found in the regions with reduced perfusion, but to a similar extent in the remote areas [16]. Conversely, an acute disassembly of myofibrils – possibly preceding the myolysis accompanying dedifferentiation – was found in both the ischemic and normally perfused remote areas in a model of prolonged partial coronary artery occlusion in chronically instrumented dogs [17].

Apart from myolysis, a possible alternative explanation for the contractile dysfunction has been suggested in an investigation by Shan *et al.* [18], reporting that a changed adrenoreceptor density in hibernating myocardium might also be involved in the mechanism of depressed myocardial function. They found that in patients with hibernating myocardium an increase in density of α-adrenergic receptor and a decreased β-adrenergic receptor density could be detected in viable segments, although, as is the case for cellular changes, a cause/effect relation is not proven. Nevertheless, this finding is important in unraveling the pathophysiology of chronic hibernation, and deserves further attention. Another relevant observation made in chronic hibernating myocardium in patients, which might explain the initiation and the maintenance of the contractile dysfunction, concerns the altered cell–cell interaction through defective gap junctions [19].

Apart from cellular changes, extracellular alterations are also present in chronic hibernating myocardium. Even in carefully selected patients, excluding the ones with prior myocardial infarction, an increase in interstitial fibrosis can be found [20]. Without other patient selection criteria, however, the amount of interstitial fibrosis varies enormously, suggesting that in many patients (micro-)infarctions coexist with hibernating segments [21]. It was found that the contractile reserve and the function after reperfusion are inversely correlated with the amount of fibrosis [22,23]. Nagueh *et al.* [23] found that viable segments (identified by dobutamine echocardiography), which recovered function after coronary bypass surgery – thus being truly hibernating segments – had less fibrosis ($2.5 \pm 4.7\%$) than segments that did not recover ($10.3 \pm 8.4\%$). The amount of fibrosis in the truly hibernating segments corresponds with earlier findings in meticulously selected patients [3]. The finding of increased amounts of fibrosis together with an incomplete recovery of function in such patients is suggestive of the occurrence of replacement fibrosis caused by myocyte loss. Therefore, a causal relationship

between cardiomyocyte dedifferentiation and apoptosis has been suggested by some investigators, thereby considering dedifferentiation as a kind of pro-apoptotic state [21] . However, it cannot be excluded that hibernation-like adaptational changes occur in the surviving border zone of infarcts, so that in some patients hibernation is the consequence rather than the cause of increased fibrosis. In favor of this hypothesis is the experimental finding that dedifferentiating cardiomyocytes appear in border zones of micro-embolization-induced micro-infarctions [13,24]. This might also explain the occurrence of cardiomyocyte cell death through apoptosis in porcine models of prolonged acute ischemia, in which significant necrosis was also present. Indeed, apoptosis is known to contribute to both acute and subacute cell death in infarctions. The latter models may be the experimental equivalent of patients with hibernating myocardium in which high levels of fibrosis and ultrastructural evidence of apoptosis were found [21]. Nevertheless, in pigs with chronically decreased coronary flow reserve, which show physiological features of hibernating myocardium without necrosis, an increase in subendocardial apoptosis was found, next to a minimal increase in connective tissue [25]. Interestingly, cardiomyocyte dedifferentiation and apoptosis were found in both areas with decreased coronary reserve as well as in normally perfused remote areas, although to a lesser extent in the latter. In patients in which myocardial infarction was meticulously excluded, only a minimal increase of connective tissue and no evidence of cardiomyocyte apoptosis was found [26]. These findings suggest that there is no causal relationship between cardiomyocyte dedifferentiation and apoptosis, but instead, that apoptosis is a temporal phenomenon occurring only at a certain stage in the development of hibernating myocardium. It can be hypothesized that at an early stage of progression of the abnormalities in function or perfusion, only part of the cell population is capable of adopting a protective phenotype, while the rest dies through apoptosis. In favor of this hypothesis are the findings that in the aforementioned porcine model the percentages of apoptosis peaked at 3 months after induction of the decreased coronary reserve [27] and that in infarct border zones dedifferentiated and apoptotic cardiomyocytes presumably belong to different cell populations [28]. This hypothesis would also be in line with the suggestion that cardiomyocyte dedifferentiation might even represent a form of programmed cell survival [5,29]. Apart from the findings that dedifferentiated cardiomyocytes are more ischemia tolerant than normally structured counterparts [6], its has recently been shown that endogenous protective mechanisms, such as increased expression of the stress protein HSP-70, are induced in cardiomyocytes in an experimental model of chronic hibernation [30]. Moreover, in pigs with hibernating myocardium, adenosine triphosphate and creatine phosphate levels were similar in dysfunctional and remote areas [31]. Undoubtedly, the development of reproducible animal models for chronic hibernating myocardium, without confounding necrosis, is of crucial importance to further unravel these issues, and might provide us with a clear insight into the role of cardiomyocyte dedifferentiation and apoptosis in hibernating myocardium.

Flow in chronic hibernating myocardium

In its original definition, chronic hibernating myocardium was described as being characterized by a chronic and severe resting myocardial blood flow. However, unlike the situation in acute ischemia where there is a close coupling between regional myocardial function and subendocardial blood flow, several studies have indicated that in the case of chronic hibernation, the decrease in blood flow is not as severe or permanent as originally thought [32,33]. Using quantitative positron emission tomography (PET), most of the more recent studies (reviewed in [34]) suggest either a normal or only moderately decreased blood flow in the dysfunctional regions. This would implicate that chronic repetitive ischemia and subsequent overlapping periods of stunning are at the basis of hibernating myocardium. It should be noted that in patient studies only relative differences in flow are evaluated, that is, in the same patient the flow in the dysfunctional areas is compared to the flow in remote non-dysfunctional regions in which an increased flow (according to the increased compensatory function) could be present. However, quantitative analysis of flow in the non-dysfunctional areas in patients and flow in normal volunteers resulted in similar values [33]. Whereas transmural differences in histological changes have consistently been demonstrated, the presence of transmural differences in blood flow, although expected, is not shown by PET because of the limited spatial resolution of this imaging technique. Observations in an experimental model of hibernating myocardium have indeed suggested the existence of such a transmural difference, the decrease in blood flow being most pronounced in the subendocardial layers [35]. Based on these and clinical studies, it is likely that chronic reversible dysfunctional myocardium can be the consequence of both sustained and repetitive underperfusion. Shen and Vatner [36] showed that chronic stunning can be at the basis of chronic dysfunctional myocardium in an experimental model where necrosis is absent and histologically identified hibernating myocardium present. In the dysfunctional regions, baseline blood flow was normal, and multiple episodes of demand ischemia during excitement and subsequent stunning were observed. The effect of repetitive stunning

was cumulative, resulting in continuously dysfunctional myocardium. Using a reproducible model of chronic coronary stenosis resulting in viable chronically dysfunctional myocardium, Fallavollita *et al.* [35] have proposed that chronic stunning and chronic hibernation form a continuum. Initially, repetitive ischemia caused chronic stunning, while resting blood flow in these dysfunctional regions was normal. This situation lasted for up to 2 months, but after 3 months, the blood flow at rest is reduced in the dysfunctional areas, leading to the physiologic findings of hibernating myocardium. The transition from stunning to hibernation seemed to occur at the time of a critical reduction in the coronary flow reserve caused by a progressive increase in stenosis severity. Moreover, it has been shown that an accelerated progression from stunning to hibernation can be induced in less than 2 weeks, when without an initial reduction in resting perfusion, an acute critical reduction in coronary flow reserve is produced [27]. Based on clinical data and the findings from experimental animal models, it is clear that viable chronically dysfunctional myocardium in patients can represent chronic stunning, chronic hibernation or a combination of both. Possibly a correlation exists between the underlying mechanism (stunning or hibernation), the degree of dysfunction, the degree of histological change, and the time frame of recovery of function after revascularization. Further research using reproducible animal models of viable chronically dysfunctional myocardium will be needed to elucidate this issue.

Conclusion

Based on the currently available clinical and experimental data it is obvious that viable chronically dysfunctional myocardium is likely to be caused by different pathophysiological mechanisms, and moreover is often confounded by the presence of irreversibly damaged tissue, from which it is not clear whether it occurs as a consequence of chronic dysfunction, or whether it is a preceding or even unrelated event. This makes a proper interpretation of the data difficult. Fortunately, several reproducible animal models are emerging, which will definitely contribute to a more adequate understanding and interpretation of the clinical counterpart.

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●● of outstanding interest

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